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MAIL STOP APPEAL BRIEF-PATENTS
PATENT
0508-1044

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Jacques Alexandre HATZFELD et al. Conf. 5595

Application No. 09/980,484 Group 1632

Filed March 25, 2002 Examiner Thaian N. Ton

PROCESS FOR THE MULTIPLICATION OF STEM CELLS

REPLY BRIEF

MAY IT PLEASE YOUR HONORS: May 7, 2008

Appellant replies to the Examiner's Answer of December 21, 2006 as follows:

THE PROPOSED COMBINATION OF HATZFELD ET AL IN VIEW OF FORTUNEL ET AL. FAILS TO RENDER OBVIOUS CLAIMS 1, 8, 9, 11, AND 31-36

Neither HATZFELD nor FORTUNEL, alone or in combination, disclose or suggest a method for maintaining a non-differentiated state of human stem cells by aadministering to human stem cells an effective amount of an inhibitor of cell development in sequential combination

with an anti-inhibitor of cell proliferation, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells (see claims 1 and 33).

Moreover, there is no recognition of repeatedly administering to human stem cells in a cell concentration of about 1 to about 10^{10} cells per ml an effective amount of an inhibitor of cell proliferation in sequential combination with an anti-inhibitor of cell proliferation to maintain the non-differentiated state of stem cells, while allowing their cell division until the amplification of the cells is sufficient to obtain a pre-determined number of cells (see claim 33).

Appellants also maintain that the HATZFELD and FORTUNEL publications are at best cumulative to what is already disclosed in the present specification. Indeed, both publications relate to the High Proliferative Potential-Quiescent ("HPP-Q") assay already disclosed in the specification beginning on page 12.

The HPP-Q assay is only a rapid differentiation culture assay used to evaluate the differentiation potential of quiescent high proliferative potential cells after activation with anti-TGFβ. Thus, the HPP-Q assay is

to be understood as a diagnostic test of the differentiation potential of cells.

HATZFELD focuses on the effect of TGFβ and anti-TGFβ on various receptors, and more particularly pertains to the use of anti-TGFβ for rendering quiescent hematopoietic progenitors sensitive to cytokine stimulation. Thus, HATZFELD does not disclose nor suggest how human stem cells can be multiplied in vitro while being maintained in a non-differentiated state, or the beneficial effect obtained of adding an inhibitor of cell development such as TGFβ for maintaining a "stem" state during cell divisions. Additionally, HATZFELD does not suggest repeatedly administering TGFβ and anti-TGFβ.

As to the excerpt "this possibility of rendering quiescent primitive progenitors responsive to optimal combinations of cytokines can be used to improve in vitro expansion of clinical samples", this excerpt from HATZFELD indicates that the purpose is for a "transient activation", (i.e., including differentiation) of stem cells by utilizing a number of different cytokine combinations. The purpose of expansion is not self-renewal (i.e., wherein a large production of undifferentiated stem cells are obtained).

Thus, contrary to the assertions of the Examiner's Answer on page 4, HATZFELD differs from the claimed invention beyond just the specific amounts of TGF-β or anti-TGFβ recited in the claims. HATZFELD fails to even disclose or suggest a process for the multiplication of stem cells, sequentially administering TGFβ and anti-TGFβ as recited in claims 1 and 33, obtaining a pre-determined number of cells as recited in claims 1 and 33, or repeatedly administering TGFβ and anti-TGFβ as recited in claim 33.

As noted above, FORTUNEL also relates to the HPP-Q assay. FORTUNEL uses the assay as a working model to study primitive quiescent haematopoietic cells. FORTUNEL fails to disclose a process for the multiplication of stem cells, sequentially administering TGFβ and anti-TGFβ as recited in claims 1 and 33, obtaining a pre-determined number of cells as recited in claims 1 and 33, or repeatedly administering TGFβ and anti-TGFβ as recited in the claimed invention.

The observation that some HPP-Q cells may maintain for at least one division their ability to return to a quiescent state in response to physiological concentrations of TGFβ does not suggest administering to

human stem cells an effective amount of an inhibitor of cell development in sequential combination with an anti-inhibitor of cell proliferation, while allowing their cell division until the amplification of the cells is sufficient to actively obtain a pre-determined number of cells.

The observation also does not lead one skilled in the art to believe that repeatedly administering TGFβ and anti-TGFβ as claimed could be utilized in a method for maintaining a non-differentiated state of human stem cells. Indeed, FORTUNEL plainly does not suggest that it would be beneficial to repeatedly administer anti-TGFβ or TGFβ in such cultures (see pg. 1872, col. 1, second paragraph and col.2, first paragraph).

Although the Examiner's Answer cites to pg. 1869, 2nd col., first full paragraph of FORTUNEL for the proposition that FORTUNEL suggests repeatedly administering TGFβ and anti-TGFβ, the passage actually relates to the effects of FL, Bfgf, and anti-TGF-β on primitive hematopoietic progenitors (see pg. 1869, col. 1, second full paragraph). Even if FORTUNEL discusses changing the culture medium, there is no evidence that the changing of the culture medium would encompass sequentially

administering TGFβ and anti-TGFβ, or repeatedly and sequentially administering TGFβ and anti-TGFβ as claimed.

Appellants further submit that it is inappropriate for the Examiner's Answer to considered that these features and others such as "returning the cells to a resting state by treatment of the cells with an inhibitor" would necessarily occur as a result of the "combined art" (see Examiner's Answer, page 4, last three lines). Indeed, either publication discloses such features.

Moreover, MPEP 2131.01 provides, "To serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (The court went on to explain that "this modest flexibility in the rule that 'anticipation' requires that every element of the claims appear in a single reference accommodates situations in which the common knowledge of technologists is not recorded in the reference; that is, where

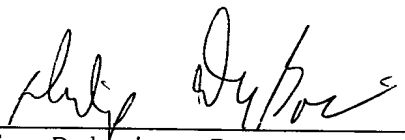
technological facts are known to those in the field of the invention, albeit not known to judges." 948 F.2d at 1268, 20 USPQ at 1749-50).

Thus, it is believed that the proposed combination of publications fail to even disclose or suggest a process for the multiplication of stem cells as set forth in claims 1 and 33, sequentially administering TGFβ and anti-TGFβ as recited in claims 1 and 33, obtaining a pre-determined number of cells as recited in claims 1 and 33, or repeatedly administering TGFβ and anti-TGFβ as recited in claim 33.

In view of the above, appellants respectfully request that the obviousness rejection be reversed.

Respectfully submitted,

YOUNG & THOMPSON



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